REVIEW ARTICLE

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Results of Liver Transplantation in the Treatment of Metastatic Neuroendocrine Tumors

A 31-Case French Multicentric Report

Y. Patrice Le Treut, M.D.,* Jean R. Delpero, M.D.,* Bertrand Dousset, M.D.,† Daniel Cherqui, M.D.,‡ Philippe Segol, M.D.,§ Georges Mantion, M.D.,‖ Laurent Hannoun, M.D.,¶ Guy Benhamou, M.D.,# Bernard Launois, M.D.,** Olivier Boillot, M.D.,†† Jacques Domergue, M.D.,‡‡ and Henri Bismuth, M.D., F.A.C.S. (Hon)§§

From the Department of Surgery, Hopital de La Conception, Marseilles; Clinique Chirurgicale,† Hopital Cochin, Paris; Department of Surgery,‡ Hopital Henri-Mondor, Créteil; Department of Digestive Surgery,§ Centre Hospitalier de Caen; Department of Digestive and Vascular Surgery,‖ Centre Hospitalier de Besançon; Department of Digestive Surgery,¶ Hopital Saint Antoine, Paris; Department of Surgery,# Hopital Bichat-Claude Bernard, Paris; Department of Surgery,** Hopital Pontchaillou, Rennes; Liver Transplant Unit,†† Hopital Edouard Herriot, Lyon; Department of Digestive Surgery,‡‡ Hopital Saint Eloi, Montpellier; and Hepato-Biliary Center,§§ Hopital Paul Brousse, Villejuif, France*

Objective

The purpose of this study was to assess the value and timing of orthotopic liver transplantation (OLT) in the treatment of metastatic neuroendocrine tumors (NET).

Summary Background Data

Liver metastasis from NET seems less invasive than other secondary tumors. This observation suggests that OLT may be indicated when other therapies become ineffective. However, the potential benefit of this highly aggressive procedure is difficult to assess due to the scarcity and heterogeneity of NET.

Methods

A retrospective multicentric study was carried out, including all cases of OLT for NET performed in France between 1989 and 1994. There were 15 cases of metastatic carcinoid tumor and 16 cases of islet cell carcinomas. Hormone-related symptoms were present in 16 cases (55%). Only 5 patients (16%) had no previous surgical or medical therapy before OLT. Median delay from diagnosis of liver metastasis and OLT was 19 months (range, 2 to 120).

Results

The primary tumor was removed at the time of OLT in 11 cases, by upper abdominal exenteration in 7 cases and the Whipple resection in 3. Actuarial survival rate after OLT was

59% at 1 year, 47% at 3 years, and 36% at 5 years. Survival rates were significantly higher for metastatic carcinoid tumors (69% at 5 years) than for noncarcinoid apudomas (8% at 4 years), because of higher tumor- and non–tumor-related mortality rates for the latter.

Conclusion

OLT can achieve control of hormonal symptoms and prolong survival in selected patients with liver metastasis of carcinoid tumors. It does not seem indicated for other NET.

Orthotopic liver transplantation (OLT) has been progressively abandoned for management of most hepatic metastasis because the unacceptably high recurrence rate does not justify the cost of the procedure and utilization of scarce donor organs.[1,2] In cases of neuroendocrine tumors (NET), metastases are frequently confined to the liver and usually slow-growing, possibly characterizing them as tumors of a less agressive nature than other secondaries.[3] However, quality of life is often poor due to pain and debility related to hepatomegaly and/or hormone production, and hepatic metastasis is the cause of death in these patients. Conventional partial hepatectomy is seldom possible since hepatic metastases are multifocal and bilateral in 90% of cases.[4] Cytoreductive surgery or "debulking" achieves 5-year survival in nearly 50% of cases, but the number of eligible patients is low.[5–7] In general, palliative treatments have been proposed for these patients, including systemic or intraarterial chemotherapy,[3,8] induced hepatic ischemia,[4] antihormone therapy using somatostatin analogue,[9] and more recently interferon therapy,[10] but survival rarely exceeds 25 to 35% at 5 years.[3,4,11] For these reasons, patients with metastatic NET are currently under "favorable consideration" for OLT.[2]

Assessment of the benefits of OLT in the treatment of metastatic NET is difficult because this entity is rare. In this regard, it should be emphasized that the term "neuroendocrine" is a generic denomination for disparate conditions[12] that can be divided into two groups, i.e., carcinoid tumors of the bronchial tree or digestive tract and noncarcinoid apudomas (NCA), essentially pancreatic islet cell carcinomas.[3,4] Failure to distinguish between carcinoids and NCA makes it difficult to interpret the results of some studies. The small number of NET also accounts for the fact that nearly all previous data come from single case reports or small unicentric series[13–25] with limited follow-up. Similarly, the three largest series reported by groups in Hanover,[2] King's College,[26] and Pittsburgh[27] have limited follow-up. The purpose of this retrospective study of the results of a multicentric French series was to define the role and timing for OLT in the treatment of metastatic NET.

Part of this work was presented at the Journées Francophones de Pathologie Digestive, Nantes, France, March 25–29, 1995.

Address correspondence and reprint requests to Dr. Y. Patrice Le Treut, Service de Chirurgie, Hopital de La Conception, 147 Boulevard Baille, 13385 Marseille Cedex 5, France.

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PATIENTS AND METHODS

Data Collection

Data were collected retrospectively from the persons in charge of the 22 liver transplantation centers in France. All centers responded. Eleven centers reported no OLT for NET, one reported eight cases, two reported five cases, one reported three cases, three reported two cases, and four reported one case. Details concerning some of the eight cases from Cochin Hospital in Paris have been previously described.[28] For each patient, the following data was compiled: pretransplant disease and treatment history, transplantation procedures, and follow-up data, including the type and delay of recurrrences and cause of deaths.

Statistical Methods

Data were expressed as medians (range) due to the small population. Comparisons were made using the nonparametric Mann-Withney U, the chi-square, and the Fisher tests. Survival curves were generated using the Kaplan Meier method and were compared using the Logrank test. A p value of <0.05 was considered statistically significant. Follow-up evaluation was made on June 30, 1995

Patients and Pretransplant Disease History

The 31 OLT for metastatic NET were performed between March 1989 and September 1994 (Table 1). There were 14 women and 17 men, with a mean age of 45 years (range, 26 to 60) at the time of OLT. In 15 cases, the primary tumor was a carcinoid: located in the ileum in 7 cases, lung in 3 cases, stomach in 2 cases, sigmoid in 1 case, rectum in 1 case, and pancreas in 1 case. In 16 cases, the tumor was a NCA: gastrinoma in 7 cases (including one gastrinoma-insulinoma and one gastrinoma-carcinoid that was part of a multiple endocrine neoplasia

Table 1. PATIENTS AND PRETRANSPLANT DATA

Patient No.	Sex	Age (yr)	Primary Tumor		Endocrine-Related Symptoms	Primary Tumor Removed Before OLT	Medical Treatment Before OLT	Months from Diagnosis of HM to OLT	Indication for OLT
			Histology	Location					
1	F	31	Carcinoid	Ileum	None	Ileocolectomy	None	12	Carcinologic
2	M	49	Carcinoid	Lung	None	Lung resection	5-FU, adriamycine, cisplatin,	21	Tumoral mass
3	M	53	Nonfunctioning	Pancreas	None	No	None	12	Tumoral mass
4	F	51	Nonfunctioning	Pancreas	Hypercalcemia	Distal pancreatectomy	IA chemotherapy	30	Carcinologic
5	F	52	Gastrinoma	Pancreas	Diarrhea, ulcers, Cushing syndrome	Distal pancreatectomy, total gastrectomy†	IA and systemic chemotherapy, octreotide	84	Hormonal syndrome
6	F	56	Carcinoid	Ileum	Carcinoid syndrome	No	5-FU-STZ, IA adriamycin	16	Hormonal syndrome
7	F	34	Carcinoid	Sigmoid	None	Left colectomy	None	2	Tumoral mass
8	F	55	Carcinoid	Ileum	Carcinoid syndrome	Ileocolectomy	Octreotide	6	Hormonal syndrome
9	M	39	Carcinoid	Rectum	None	Transanal tumorectomy	5-FU-STZ	52	Tumoral mass
10	F	42	Gastrinoma	Pancreas	Ulcers, hypercalcemia	No	None	15	Tumoral mass
11	M	39	Nonfunctioning	Pancreas	None	No	5-FU-mitomycin	4	Tumoral mass
12	M	30	Carcinoid	Pancreas	Carcinoid syndrome	No	Chemotherapy, octreotide	7	Hormonal syndrome
13	F	42	Nonfunctioning	Pancreas	None	No	5-FU, radiotherapy	19	Carcinologic
14	M	42	Carcinoid	Lung	Carcinoid syndrome	Lung resection	5-FU-STZ	8	Carcinologic
15	M	53	Carcinoid	Stomach	None	No	None	120	Tumoral mass
16	M	51	Nonfunctioning	Pancreas	None	No	5-FU-STZ	6	Carcinologic
17	M	44	Gastrinoma (MEN 1)	Pancreas	Diarrhea, ulcers	Distal pancreatectomy	Chemotherapy, octreotide	30	Tumoral mass
18	F	43	Nonfunctioning	Pancreas*	None	No	None	2	Tumoral mass
19	F	57	Carcinoid	Meckel*	None	No	Adriablastin	6	Fibrolamellar carcinoma
20	F	35	Gastrinoma	Unknown	Diarrhea, ulcers	No	Chemotherapy, octreotide	60	Tumoral mass
21	M	49	Gastri-insulinoma	Pancreas	Diarrhea, ulcers, hypoglycemia	Whipple resection, total gastrectomy	IA and systemic chemotherapy, octreotide	108	Hormonal syndrome
22	F	48	Carcinoid	Ileum	Carcinoid syndrome	Ileal resection	Chemotherapy	30	Hormonal syndrome
23	M	44	Nonfunctioning	Pancreas	None	Whipple resection	5-FU-STZ, octreotide	18	Carcinologic
24	F	51	Nonfunctioning	Pancreas	None	No	None	3	Carcinologic
25	M	50	Glucagonoma	Pancreas	Diabetes	Upper abdominal exenteration†	None	24	Hormonal syndrome
26	M	60	Carcinoid	Ileum	Carcinoid syndrome	Ileal resection†	Octreotide	96	Hormonal syndrome
27	M	26	Carcinoid	Ileum	Carcinoid syndrome	Ileal resection†	5-FU-STZ, octreotide	34	Hormonal syndrome
28	M	49	Carcinoid	Lung	Carcinoid syndrome	Lung resection	5-FU-STZ, octreotide	24	Hormonal syndrome
29	M	42	Carcinoid	Stomach	None	Subtotal gastrectomy	IA and systemic chemotherapy, octreotide	24	Variceal bleeding
30	M	34	Gastrinoma	Pancreas	Diarrhea, ulcers	No	5-FU-STZ	18	Hormonal syndrome
31	F	54	Gastrinoma	Pancreas	Diarrhea	No	5-FU-STZ, adriamycin	25	Tumoral mass

HM = hepatic metastasis; 5-FU = 5-fluorouracil; STZ = streptozotocin; IA = intra-arterial; OLT = orthotopic liver transplantation.

* Location discovered after OLT.

† Cases with concomitant or repeated liver resection.

type 1 (MEN-1) syndrome), glucagonoma in 1 case, and nonfunctioning islet cell carcinoma in 8 cases (including two that could be considered as subclinical glucagonoma and one as subclinical insulinoma).

NET was associated with symptomatic hormonal syndrome (gastrointestinal, metabolic, or vasomotor) in 16 cases, or 55%. Typical carcinoid syndrome was observed in 8 of 15 cases, or 53%. Diarrhea and/or recurrent gastroduodenal ulcers were observed in 7 of 16 NCA, or 44%. Hypercalcemia was observed in two cases: diabetes in one case and severe paraneoplastic Cushing syndrome in one case. In 18 cases, there was an abnormal elevation of plasma levels of the following peptides and/or amines: serotonin in 10 cases, gastrin in 5 cases (including 4 associated with elevated ACTH, insulin, parathyroid hormone, and prolactin), glucagon in 2 cases, and parathyroid hormone in 1 case.

Resection of the primary tumor had been performed prior to OLT in 17 cases, or 54%, Resection was performed more often in patients with carcinoid tumors (11 of 15 cases, or 73%) than NCA (6 of 16 cases, or 38%) ($p < 0.05$). The procedures used are summarized in Table 1. One or more hepatectomies for metastasis had been performed in four patients, including three complete single stage resections and one incomplete two-stage resection. In 11 cases, resection of the primary tumor was performed at the time of OLT. In two cases, the primary tumor was identified only after OLT: one nonsecreting carcinoid (8 mm) on a Meckel's diverticulum that was resected at 6 months after OLT and one nonfunctioning apudoma (7 mm) in the head of the pancreas resected 18 months after OLT. In the remaining case, the primary gastrinoma was probably a positive lateroduodenal lymph node that was removed during OLT.

In five cases, hepatic metastasis was diagnosed before detection of the primary tumor, with a delay of 6, 18, 36, 60, and 120 months. In 22 cases, hepatic metastasis was present at the time of diagnosis of the primary tumor. In four cases, hepatic metastasis occured after the diagnosis of the primary tumor, with a delay of 18, 24, 25, and 72 months. Hepatic metastasis was multiple and bilateral in 27 cases, and the remaining four cases involved hepatic recurrence after previous hepatectomy. Systemic or intraarterial chemotherapy had been administered prior to OLT in 23 cases, or 74%. The most common protocol was a 5FU-streptozotocine combination. Most patients received specific hormonal inhibitors using octreotide (carcinoids) or omeprazole (gastrinomas). Five patients, or 16%, did not undergo surgery or chemotherapy prior to OLT.

The median time from diagnosis of hepatic metastasis to OLT was 19 months (range, 2–120). There was no significant difference in the median diagnosis-to-OLT delay for patients with carcinoid tumors (21 months, with a range of 2 to 120) and patients with NCA (19 months, with a range of 2 to 108). The indication for transplantation was hormonal syndrome poorly controlled by medical treatment in 11 cases (35%) (carcinoid syndrome in 7 cases and diarrhea, ulcers, hypercalcemia, or some combination thereof in the other 4 cases). The median delay from diagnosis of hepatic metastasis to OLT in this group was 24 months. In another 11 cases (35%), transplantation was indicated by pain or debility associated with tumor bulk. The median delay from diagnosis of hepatic metastasis to OLT in this group was 21 months. In eight cases, OLT was performed with the intent to cure patients with stable bilobar invasion without hormonal syndrome or debilitating hepatomegaly, including one patient whose pretransplant diagnosis was fibrolamellar carcinoma. The median delay from diagnosis of hepatic metastasis to OLT in this group was 10 months. In the remaining patient, OLT was performed in emergency for active variceal bleeding related to secondary sclerosing cholangitis with portal hypertension due to chemoembolization.

RESULTS

Transplantation Procedures

Total hepatectomy with lymphadenectomy of the hepatoduodenal ligament (or beyond) was performed in all cases (Table 2). Extrahepatic resection was performed in 14 cases, or 45%: *en bloc* diaphragmatic resection in 3 cases and concomitant resection of the primary tumor in 11 cases, including ileal resection in one case, Whipple resection in 3 cases, and upper abdominal exenteration with removal of the stomach, spleen, duodenopancreatic complex, and variable amounts of the colon in 7 cases. After upper abdominal exenteration, liver replacement was associated with duodenum pancreas *en bloc* ("cluster procedure"[29]) in three cases and intraportal injection of pancreatic islet cells[30] in one case. Biliary reconstruction was achieved by bilioenteric anastomosis in 17 cases and biliobiliary anastomosis in 11 cases. Biliary anastomosis was not performed in the three cases involving composite hepatic duodenal and pancreatic graft. Venovenous bypass was used in 18 cases, or 58%.

The median duration of cold ischemia was 10 hours (range, 5.6 to 20). Overall median procedure duration was 10 hours (range, 5.5 to 20). Median procedure duration was 9 hours (range, 5.5 to 17) for simple hepatectomy (21 cases) and 11 hours (range, 8 to 20) for hepatectomy associated with extensive visceral resection as in the Whipple resection or upper abdominal exenteration (10 cases). Procedure duration was 10, 12, and 14.5 hours for the three cases of composite

Table 2. OPERATIVE DATA AND CLINICAL OUTCOME

Case No.	Surgery in Addition to the OLT*	Specimen Weight (g)	Metastatic LN	Major Surgical and Medical Complications	Postoperative Stay (days)	Site of Recurrence	Status	Follow-up (mo)
1	None	1390	—	Subcapsular hematoma	26		Alive	77
2	None	5400	—		25	Bone (spine)	Died	41
3	Upper abdominal exenteration†	4280	Yes	Acute pancreatitis, peritoneal bleeding	Died, 18		Died	1
4	None	2750	—		22	Rapid generalization	Died	6
5	Diaphragmatic resection	—	—	Peritoneal bleeding, PV thrombosis, re-OLT (D12)	Died, 83		Died	3
6	Ileal resection	2900	Mesenteric		47	Mesenteric LN	Alive	70
7	None	6750	Hilar	Peritoneal bleeding, HA aneurysm	37	Rapid generalization	Died	2
8	None	—	No		15		Alive	70
9	None	13000	No	Chronic rejection: re-OLT at 5 mo	32	Bone, liver	Alive	70
10	Upper abdominal exenteration	7500	No		30	bone (spine)	Died	30
11	Upper abdominal exenteration	5100	Yes	Ileocolic anastomotic fistula	76		Died	4
12	Upper abdominal exenteration	—	—	Peritoneal bleeding, re-OLT for PNF (D4)	Died, 6		Died	0
13	Upper abdominal exenteration†	1400	No	Peritoneal bleeding, acute pancreatitis	Died, 6		Died	0
14	None	3300	—	Peritoneal bleeding, CMV pneumonitis	28	Bone, generalization	Alive	63
15	Upper abdominal exenteration	4000	No	Esojejunal anastomotic fistula	57		Died	10
16	Upper abdominal exenteration†	1320	Yes, 13/15	Enteric fistula, unexplained sepsis	Died, 74		Died	3
17	Diaphragmatic resection	—	Celiac		24		Died	16
18	None	8900	Hilar		30	Bone, ovaries, abdominal LN	Alive	51
19	None	1412	No		21		Alive	49
20	None	—	Duodenal	Chronic rejection: re-OLT at 7 mo	16		Died	8
21	None	3350	Hilar	Peritoneal bleeding	39	Periaortic LN	Died	39
22	None	1233	No	Biloma	45		Alive	37
23	None	1800	No		21	Bone, lungs	Died	17
24	Whipple resection	2580	Yes	Acute rejection (OKT3)	47	Peritoneum, liver	Died	7
25	None	—	—	Peritoneal bleeding, PV thrombosis	Died, 12		Died	0
26	None	—	Periaortic	HA thrombosis, biliary stricture, acute rejection (FK 506)	15		Alive	32
27	None	1620	Yes, 13		22	Peritoneum (resected)	Alive	23
28	None	2200	No		26		Alive	23
29	Diaphragmatic resection	—	—		33		Alive	21
30	Whipple resection	2800	Yes	Pancreatic fistula, digestive hemorrhage	35		Died	5
31	Whipple resection	4500	Yes	Acute rejection (OKT3, FK 506)	45		Alive	10

OLT = orthotopic liver transplantation; PV = portal vein; HA = hepatic artery; PNF = primary nonfunction; LN = lymph nodes.
* Except for node dissection.
† Cases with duodenum pancreas graft.

hepatic duodenal and pancreatic graft. Median transfusion requirements were 10 U of red blood cells (range, 0 to 130) and 20 U of plasma (range, 0 to 104) in the overall population, 6 U of red blood cells (range, 0 to 45) and 12 U of plasma (range, 0 to 56) in the group that underwent simple hepatectomy, and 22 U of red blood cells (range, 5 to 130) and 50 U of plasma (range, 16 to 104) in the group in which hepatectomy was associated with resection of adjacent organs other than the diaphragm or small intestine.

The weight of the surgical specimens was indicated in 23 of the 31 cases. Overall median weight was 2896 g (range, 1230 to 13,000). The median weight of the surgical specimen was 2500 g in patients transplanted for hormonal syndrome, 5400 g in patients transplanted mainly for hepatomegaly, and 1980 g for patients transplanted for other reasons. There was lymph node involvement of the hepatoduodenal ligament or beyond in 13 cases, and no lymph node involvement in 10 cases. In the remaining eight cases, this information was not mentioned.

Follow-Up

Immunosuppression included a double regimen using cyclosporin and corticosteroids or a triple regimen using cyclosporin, corticosteroids, and azathioprine in all patients except one liver-pancreas recipient in whom prophylactic OKT3 was used (Table 2). Acute corticosteroid-resistant rejection occurred in three cases requiring OKT3 and/or FK 506. Chronic rejection occurred in two cases requiring retransplantation at 5 and 7 months postoperatively.

Postoperative Mortality and Morbidity

Six patients, or 19%, died after surgery. The cause of death was persistent intraabdominal hemorrhage in five of six cases—associated with acute pancreatitis in two cases, thrombosis of the portal vein in two cases, and primary nonfunction of the graft in one case. In the remaining patient, death resulted from disseminated bacterial and viral infection. The postoperative mortality rate was 7% for carcinoid tumors (1 of 15 cases) and 31% for NCA (5 of 16 cases). This difference was not significant. Postoperative mortality was 57% (4 of 7 cases) in patients who underwent upper abdominal exenteration, and 100% (3 of 3 cases) in patients who underwent duodenum-pancreas replacement. One or more major surgical complications occurred in 15 patients, usually requiring further surgery. In two of these patients, retransplantation for early graft failure was performed at days 4 and 12. Major complications occurred in 7 of the 10 cases, or 70%, involving major extrahepatic resection (exenteration or Whipple resection) and in 8 of the 21 cases, or 38%, involving hepatectomy alone (NS). The median duration of postoperative stay was 29 days (range, 15 to 76).

Long-Term Results

Twenty-five patients were discharged. None was lost to follow-up. Twelve patients (3 with carcinoids and 9 with NCAs) died after discharge. The cause of death was a delayed technical or other nontumor complications in 4 cases, including two fatal hypoglycemic events associated with severe malnutrition at months 4 and 10 after supramesocolic exenteration, one massive digestive hemorrhage due to rupture of the splenic artery 5 months after OLT combined with Whipple resection, and one hepatic artery thrombosis after retransplantation at postoperative month 7 for chronic rejection. One death due to diabetic coma with intravascular coagulopathy occurred 30 months after exenteration for gastrinoma in a patient with multiple spine metastases. Thus, all seven patients who underwent upper abdominal exenteration died from immediate or delayed procedure-related complications. Seven patients died of tumor recurrence within 2 to 41 months after OLT. Bone metastases were observed in almost all cases associated with liver, lymph node, and peritoneal involvement. It should be emphasized that six of the eight patients who died from or with tumor recurrence presented metastatic NCA.

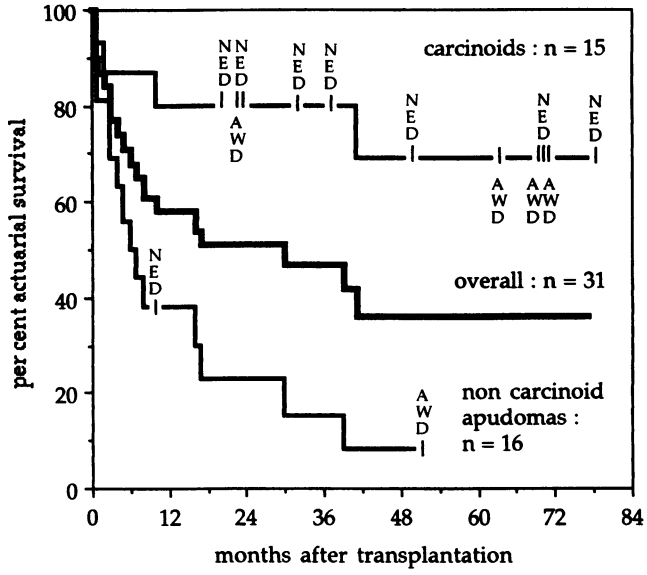

Figure 1. Survival after OLT for metastatic neuroendocrine tumors. NED = nonevidence of disease; AWD = alive with disease. Carcinoids *vs.* noncarcinoid apudomas; $p < 0.001$.

In mid 1995, 13 patients (11 with carcinoids and 2 with NCAs) were living. Eight had no biochemical or imaging evidence of recurrent disease at follow-ups of 10 to 77 months. The remaining 5 patients with follow-ups of 23 to 70 months had evidence of metastasis, including bone and spine involvement in 3 cases, abdominal lymph node involvement in 1 case, and peritoneal involvement (treated by debulking 15 months after OLT) in 1 case. The diagnosis in four of these five patients was carcinoid tumors.

Overall Patient Survival

Median follow-up in the 31 patients of this series was 57 months (range, 10–77). Median survival was 30 months after transplantation. Actuarial survival was 58%, 51%, 47%, 36%, and 36% at 1 to 5 years, respectively (Fig. 1). Five patients survived >60 months, including two who were disease-free in mid-1995. The survival rate at 5 years after diagnosis of liver invasion was 57%. Overall disease-free survival was 45%, 29%, and 17% at 1, 3, and 5 years after OLT, respectively (Fig. 2). For metastatic carcinoid tumors, the survival rate was 80%, 80%, and 69% at 1, 3, and 5 years, respectively. For metastatic NCA, the survival rate was 38%, 15%, and 8% at 1, 3, and 4 years, respectively. The longest survival in the NCA group was 51 months after OLT. The difference in overall (Fig. 1) and disease-free survival (Fig. 2)

between patients with carcinoid tumors and NCA was highly significant ($p < 0.001$).

DISCUSSION

This multicentric study, including all OLT for metastatic NET performed in France between 1989 and 1994, is the largest reported series and is of epidemiologic value given the rarity of this therapeutically challenging disease. Two disappointing findings were the low overall survival at 5 years (36%) and low disease-free survival at 5 years (17%). Interestingly, however, survival rates were significantly higher for carcinoids (69% at 5 years) than NCA. Two explanations can be proposed for this difference. The first is lower postoperative mortality in patients with carcinoid tumors (7%), and the second is that recurrences of carcinoid tumors, albeit occurring at the same rate as in the NCA group, were more compatible with long-term survival. Three patients who presented carcinoid tumors in this series are living at 5 years after OLT despite recurrence. In this regard, it should be emphasized that the median duration of pretransplant history of hepatic metastasis was not significantly different in the two groups.

Our perusal of the literature (1989 to 1996) turned up 37 cases of OLT for metastatic NET with sufficient data for analysis (Table 3). More than half of these cases involved symptomatic hormonal syndrome. Postoperative mortality in this compiled series was 11% (4 of 37 cases). Eleven other patients died during follow-up, including 10 from recurrence, with a median delay of 10 months after OLT (range, 5 to 67). Twenty-three patients are still living, with a median follow-up of 16 months (range, 4 to 106), including three presenting recurrence. Cumulative survival for these 37 patients was estimated by the Kaplan Meier method based upon the duration of survival specified for each patient in each report. Actuarial patient survival was 66%, 56%, 46%, 46%, and 46% at 1–5 years after OLT, respectively. These rates are slightly higher than those reported in our series, but it should be noted that follow-up was limited in the compiled series, with only 5 of 37 patients still being at risk at 3 years. The 3-year survival rate was the same as in our series. In the compiled series, there were 17 metastatic carcinoid tumors originating from the ileum in 6 cases, pancreas in 3 cases, lung in 3 cases, stomach in 2 cases, duodenum in 1 case, anus in 1 case, and an undetermined location in 1 case, and 20 NCA, including 14 pancreatic islet cell carcinomas. Surprisingly, the survival rate was significantly higher for NCA than for carcinoids (83% at 2 years versus 34% at 2 years; log rank = 9.49, $p < 0.01$) due to high postoperative mortality and recurrence rate in the carcinoid group.

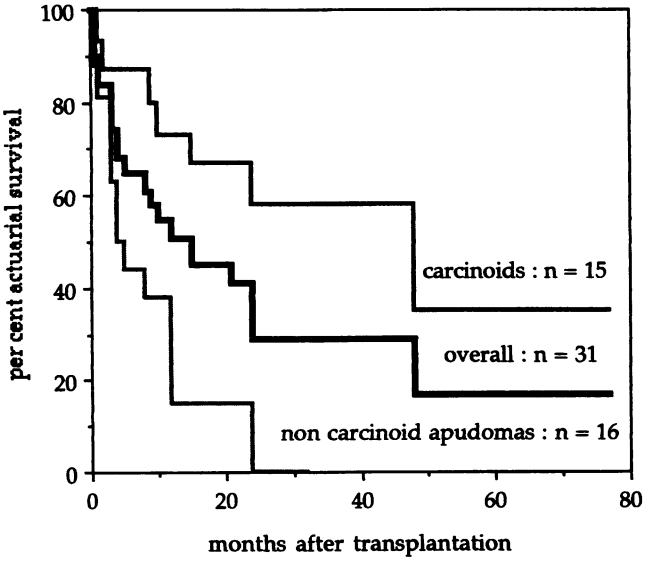

Figure 2. Disease-free survival after OLT for metastatic neuroendocrine tumors. Carcinoids *vs.* noncarcinoid apudomas; $p < 0.001$.

The largest previously reported unicentric series were the King's College series, the Hanover series, and the Pittsburgh series. In the King's College series, which was included in the compiled series,[26] there were a total of 11 cases, including 6 patients with carcinoids and 5 patients with NCAs. Median survival after OLT was not significantly different in the carcinoid group and NCA group (20 months versus 18 months), but recurrence was observed in 5 of the 6 patients with carcinoids versus only 1 of the 5 patients with NCAs. However, the fact that median time from initial diagnosis to OLT was longer in the carcinoid group than in the NCA group (71 months versus 16 months) raises the possibility that OLT was carried out later in the course of the disease in the former than latter. The Hanover group reported 11 patients with OLT for metastatic NET, including 9 patients with carcinoids. Despite discouraging initial results[13], actuarial survival was 81% at 1, 3, and 5 years.[2] However, it should be stressed that only three patients in this series had follow-ups of >3 years. In the Pittsburgh series, the best results after the cluster procedure were obtained in the subgroup of 14 patients with NET. The number of carcinoids and NCAs was not mentioned. Survival was 64% at 1 and 3 years.[27]

The 5-year survival rate after nontransplant treatment of NET ranges from 25 to 35%.[3,4,11] However, this figure cannot be compared to the results of liver replacement, which is generally performed in symptomatic patients only after other therapies become ineffective. In our series, 71% of patients were transplanted due to symptoms related to tumor bulk, hormone secretion, or both. Only 16% had not undergone any medical or surgical treatment prior to OLT. The 5-year survival after diagnosis of he-

Table 3. SERIES OF ORTHOTOPIC LIVER TRANSPLANTATION FOR NEUROENDOCRINE TUMORS COMPILED FROM THE LITERATURE (1989–1996)

Reference (yr)	Patient Sex, Age (yr)	Primary Tumor Type	Location	Endocrine-Related Symptoms	Status	Follow-up (mo)
Ringe et al.[13] (1989)	F, 59	Carcinoid	Ileum	Yes	DOD	6
	F, 18	GRFoma	Jejunum	—	Alive, NED	4
	F, 51	Carcinoid	Ileum	Yes	Died after operation	0
Makowka et al.[15] (1989)	M, 41	Glucagonoma	Pancreas?	No	Alive, NED	41
	F, 52	Carcinoid	Ileum	No	Died after operation	2
	F, 41	Glucagonoma	Pancreas*	Yes	Alive, NED	23
	M, 39	Carcinoid (+CCA)	Ileum*	Yes	DOD (CCA)	9
	M, 45	Gastrinoma	Pancreas*	Yes	DOD	10
Mieles et al.[16] (1990)	F, 37	Carcinoid	Duodenum*	—	Alive, NED	11
	M, 27	Carcinoid	Stomach*	—	Died after operation	0
	F, 41	Carcinoid	Pancreas*	—	Alive, NED	6
Olthoff et al.[17] (1990)	—	Neuroendocrine	Pancreas*	—	Alive, NED	5
Bramley et al.[18] (1990)	F, 41	VIPoma	Pancreas*	Yes	Alive, NED	12
Alsina et al.[19] (1990)	M, 51	Glucagonoma/carcinoid	Pancreas*	No	Alive, recurrence	34
Schweizer et al.[20] (1993)	M, 47	Nonfunctioning	Pancreas*	No	Alive, NED	26
	F, 46	Neuroendocrine	—	No	Alive, NED	10
Gulanikar et al.[21] (1991)	F, 55	Carcinoid	Stomach*	Yes	DOD	5
Lobe et al.[22] (1992)	F, 11	Insulinoma	Pancreas*	Yes	Alive, NED	15
Frilling et al.[23] (1994)	M, 52	Carcinoid	Lung	Yes	Alive, NED	10
Curtiss et al.[24] (1995)	F, 40	Nonfunctioning	Pancreas*	No	Alive, NED	30
	M, 52	VIPoma	Pancreas	Yes	Alive, NED	20
	M, 56	Nonfunctioning	Pancreas*	No	Alive, NED	12
Routley et al.[26] (1995)	54	Carcinoid	Anus	No	Alive, recurrence	41
Arnold et al.[14] (1989)	51	Carcinoid	Unknown	No	DOD	25
	46	Carcinoid	Ileum	Yes	Alive, NED	10
	56	Carcinoid	Ileum	Yes	DOD	67
	59	Carcinoid	Lung	Yes	DOD	8
	50	Carcinoid	Lung	Yes	DOD	14
	48	Apudoma	Unknown	No	Alive, recurrence	28
	37	Apudoma	Lung	No	Alive, NED	18
	43	Apudoma	Unknown	No	Alive, NED	106
	55	Apudoma	Pancreas	Yes	Died, NED	8
	42	Apudoma	Pancreas	Yes	Alive, NED	16
Anthuber et al.[25] (1996)	F, 34	Nonfunctioning	Kidney	No	DOD	33
	F, 62	Glucagonoma	Pancreas*	—	DOD	7
	M, 52	Carcinoid	Pancreas*	—	Died after operation	0
	M, 57	Carcinoid	Pancreas	—	DOD	5

DOD = died of recurrent disease; NED = no evidence of disease; CCA = cholangiocarcinoma; GRF = growth hormone-releasing factor; VIP = vasoactive intestinal polypeptide.
* Primary tumor removed at the time of orthotopic liver transplantation.

patic metastasis in our OLT series was 57%. This compares favorably with conventional treatment.

Results of OLT could be improved by reducing surgical mortality and recurrence rate. In our series, the morbidity of upper abdominal exenteration was unacceptably high; four of seven patients who underwent this procedure died of surgical complications, and the remaining three died of severe physiologic disturbances related to total resection of the stomach and pancreas. Despite much greater experience in the Pittsburgh series, the mortality rate from causes other than tumor recurrence was still 28% after cluster procedure.[27] Based on these observations, it seems advisable to use a resection technique that preserves part of the stomach and/or pancreas: partial gastrectomy, distal pancreatectomy, or Whipple resection with or without anastomosis of the pancreatic remnant. When possible, these methods seem to be safer than composite liver-pancreas-duodenum graft, which led to fatal postoperative complications in all three cases in our series. Another way to improve postoperative recovery may be two-stage treatment of the primary tumor and the hepatic metastasis.[7,26,28] This strategy violates the rule that *en bloc* resec-

tion should be performed for cancer patients but offers the following three advantages: 1) thorough assessment of lesions during the first procedure to rule out extrahepatic tumor invasion; 2) sufficient time for medical treatment of liver metastasis and observation of metastatic evolution; and 3) lower risk of the transplantation procedure, especially in patients with pancreatic NET. However, the risk of OLT after extensive dissection of the upper mesocolic region should not be underestimated.[28]

To reduce the risk of recurrence after transplantation, a thorough pretransplant evaluation is needed to exclude the presence of extrahepatic tumor deposits and thus ensure that the OLT can eradicate the whole disease. It should be underlined that the next most frequent site of distant metastasis after the liver is bone.[3] Several patients in our series and in those reported previously[15,21,25,26] presented early metastasis of the bone, which was often the first site of recurrence. In this regard, it should be noted that somatostatin receptor scintigraphy appears highly sensitive for the detection of lung and bone metastasis of NET.[23,25,28,31,32]

Whether all types of metastatic NET should be considered for OLT remains controversial. Unlike the previous cases in the compiled series, our results indicate that OLT achieves better results for carcinoid tumors than for NCA. However, it should be noted that carcinoid tumors of the pancreas herald shorter survival than midgut or hindgut carcinoids.[11,25] In this regard, it has stated that carcinoid tumor of the pancreas should be considered and managed as islet cell carcinoma producing serotonin.[3] Some authors have suggested that early recurrences of carcinoid tumors after OLT could be due to a combination of immunosuppression and the presence of aneuploid cell lines in the primary tumor.[21] The second condition is probably uncommon because most carcinoid tumors have a diploid DNA profile, indicative of low malignant potential,[21,33] but DNA analysis by flow cytometry could be useful for patient selection.

As regards the timing of transplantation in patients with tumors of low malignant potential whose spontaneous survival can be long, we agree with previous authors[6,7,24,25,26] that OLT may be indicated 1) for patients with symptoms due to hepatomegaly or hormone production, 2) following resection of the primary tumor, and 3) after failure of other available treatments despite possible risks and side effects. Patients with carcinoid tumors of the lung and gastrointestinal tract who often fulfill these criteria could be an indication of choice. Our results suggest that OLT may not be indicated in other cases.

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